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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,023	06/28/2001	Vladmir R. Muzukantov	PENN-0749	7329

26259 7590 01/16/2003

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EXAMINER
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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/16/2003 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/762,023	Muzukantov et al.
Examiner	**Art Unit**
DiBrino, Marianne	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 7, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above, claim(s) *1-4* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5-8* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6 filed 2/4/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's response filed 11/7/02 (Paper No. 9) is acknowledged and has been entered.

Claims 1-8 are pending.

2. Applicant's election with traverse of Group II (claims 5-8) in Paper No. 9 is acknowledged.

The traversal is on the ground that there is a special technical feature because Bowes et al showed that the combination of tPA and anti-ICAM Ab did not work better than each alone in reducing neurological damage. Applicant argues the remainder of the articles individually.

Applicant's arguement has been considered, but is not deemed persuasive because Bowes et al teach "..the combination of a[anti]-ICAM-1...and tPA...significantly improved neurologic outcome even though neither substance was effective alone..." (Abstract) and Imaizumi et al teach "...1A29 used in this study are neutralizing antibodies that specifically inhibit...ICAM-1 on vascular endothelial cells..." (Page 1853, paragraph bridging columns 1 and 2). Therefore, claim 1 deos not provide a special technical feature and so the instant claims 1-8 lack an inventive step and therefore lack Unity of Invention.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-4 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 5-8 are currently being examined.

3. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60/095,240. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

The first sentence of the specification should refer to the provisional application using language such as: This application claims the benefit of U.S. Provisional Application No. 60/____, filed ____. See MPEP 1302.04. If a statutory reference is included in this statement, if must be to 35 USC 119(e) and not to 35 USC 120.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Applicant is advised that the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999 were published subsequent to the prior Office Action and the claims have been examined in view of these guidelines. The following rejection is set forth herein.

Claim 5- 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed method for dissolution of fibrin clots or prevention of the intravascular coagulation in the pulmonary vasculature comprising administering a fibrinolytic or anticoagulant in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium.

The instant claims encompass a method of treatment in vivo using a non-internalizable antibody that is not an anti-ICAM-1 or a method of prevention using any antibody, including an anti-ICAM-1 antibody. There is insufficient disclosure in the specification on such an antibody.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The instant specification (paragraph spanning pages 3 and 4) discloses that mAb 1A29 is an anti-ICAM-1 antibody which is non-inernalizable. The specification discloses that "It has now been found that monoclonal antibodies against...ICAM-1 bind effectively to the endothelial cells without subsequent internalization" (page 4 at lines 8-10). The specification discloses antibodies against endothelial antigens such as ACE, thrombomodulin and E-selectin which effectively bind to the pulmonary endothelial vasculature and which effectively deliver drugs to the site (paragraph spanning pages 2 and 3). Evidentiary references on page 3 of the instant specification at lines 9-15 teach that endothelial cells internalize antibodies against thrombomodulin, E-selectin and PECAM, 3 pev antigens.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "non-inernalizable antibody" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being non-internalizable. It does not specifically define any of the proteins that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by the property of being "non-internalizable" does not suffice to define the genus because it is only an indication of a general property the antibody has. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

There are insufficient relevant identifying characteristics disclosed.

6. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dissolution of fibrin clots by administering a non-inernalizable antibody to ICAM-1 and a fibrinolytic or anti-coagulant, does not reasonably provide enablement for the claimed method of treatment in vivo using a non-internalizable antibody that is not an anti-ICAM-1, nor for the claimed method of prevention using any non-internalizable antibody, including anti-ICAM-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope

with these claims.

The instant specification (paragraph spanning pages 3 and 4) discloses that mAb 1A29 is an anti-ICAM-1 antibody which is non-internalizable. The specification discloses that "It has now been found that monoclonal antibodies against...ICAM-1 bind effectively to the endothelial cells without subsequent internalization" (page 4 at lines 8-10). The specification discloses antibodies against endothelial antigens such as ACE, thrombomodulin and E-selectin which effectively bind and accumulate in the vasculature and which effectively deliver drugs to the site (paragraph spanning pages 2 and 3). The specification further discloses uptake and accumulation of anti-ICAM-1 mAb 1A29 in rat lung intravascular endothelial surface (pev) and functional activity of tPA in isolated rat lungs so treated (pages 15 and 16).

The specification does not disclose how to treat with a non-internalizable antibody to an antigen on the luminal surface of pev, nor how to prevent using any non-inernalizable antibody to an antigen on pev luminal surface. Evidentiary references on page 3 of the instant specification at lines 9-15 teach that endothelial cells internalize antibodies against thrombomodulin, E-selectin and PECAM, 3 pev antigens.

There is no guidance in the specification as to what makes a non-internalizable antibody to such an antigen, or which pev antigens are suitable candidates for non-inernalizable antibody production, and subsequently no guidance on how to treat or prevent as claimed. Because of this lack of guidance, the extended experimentation that would be required to determine which antibodies are non-internalizable, which antigens are suitable targets and which antibodies would be effective to treat or prevent, it would require undue experimentation for one of skill in the art to arrive at other antibodies other than anti-ICAM-1 that have functional activity in treatment or any antibodies which are sufficient to prevent. The enablement provided by the specification is not commensurate with the scope of the claims. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 5 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bowes et al (Neurology, 1995, IDS reference) in view of Imaizumi (Transpl Proc, 1994, IDS reference) and further in view of Mulligan et al (Amer. J. Pathol, 1993, IDS reference) and Panes et a (Amer. J. Physiol., 1995, IDS reference).

Bowes et al teach that administration of an anti-ICAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes et al also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated.

Bowes et al do not teach a method for targeting and prolonging association of a selected drug to the luminal surface of pulmonary vascular endothelium comprising administering to an animal a selected drug in combination with a non-internalizable antibody which binds to the luminal surface of the endothelium.

Imaizumi teaches a method of administration of mouse anti-rat mAb 1A29 (anti-ICAM-1)inhibits ICAM-1 on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury. Imaizumi teaches that impairment of reperfusion injury is closely associated with vascular endothelial cell damage by neutrophils. Imaizumi further teaches that in flowing blood, neutrophils do not adhere to vascular endothelial cells in the normal state; adhesion of neutrophils to vascular endothelial cells is necessary to induce vascular endothelial cell damage after ischemia and reperfusion, and an increase in the expression of adhesion molecule (especially page 1853, column 1). Imaizumi teaches an increase in the expression of adhesion molecules in vascular endothelial cells activated by reperfusion and a resultant increase in the binding to neutrophils.

Mulligan et al teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated.

Panes et al teach that ICAM-1 is consitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression.

It would have been prima facie obvious at the time the invention was made to have substituted the mAb 1A29 of Imaizumi or of Mulligan et al for the anti-ICAM-1 mAb in the composition of Bowes et al and to have used the combined composition in the method of Imaizumi given the teaching of Panes et al that ICAM-1 is consitutively expressed on vascular endothelium. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat ischemia and pulmonary reperfusion injury in rats.

9. Claims 7 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bowes et al (Neurology, 1995, IDS reference) in view of Imaizumi (Transpl Proc, 1994, IDS reference) and further in view of Mulligan et al (Amer. J. Pathol, 1993, IDS reference) and Panes et a (Amer. J. Physiol., 1995, IDS reference) as applied supra and further in view of Torchilin et al (J. Contr. Rel., 1985, IDS reference), Muzykantov et al (BBA, 1986, IDS reference) and Muzykantov et al (Amer J Physiol, 1996, IDS reference).

The combination of Bowes et al, Imaizumi, Mulligan et al and Panes et al has been discussed supra.

The reference teachings differ from the instant claims in that they do not teach conjugation of the selected drug to the antibody either before or after administration by chemical modification.

Runge et al teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation, i.e., chemical modification, to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract).

Torchilin et al teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA.

Muzykantov et al (BBA, 1986) teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation.

Muzykantov et al (Amer J Physiol, 1996) teach targeting of drugs to the pulmonary vascular endothelium using antibody. In addition, Muzykantov et al teach chemical modification, i.e., using the streptavadin-biotin system, of a mAb to recognize a target molecule localized on the vascular endothelium.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered a thrombolytic enzyme drug such as tPA with 1A29 as discussed supra, and further by conjugating tPA to a mAb (such as 1A29) as taught by Torchilin et al, or for Runge et al and Muzykantov et al for fibrolytic agents or for other molecules recognizing mAb specific for target molecules on vascular endothelium, either directly or indirectly by chemical modification as taught by Muzykantov et al or Runge et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to effectively target tPA as taught by Torchilin et al and Muzykantov et al and Runge et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640/Technology Center 1600
January 13, 2003

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